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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/002,802	11/02/2001	Michael D. Uhler	UM-06669	3812

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/002,802	UHLER, MICHAEL D.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004 and 04 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-25,27-32 and 34-42* is/are pending in the application.

4a) Of the above claim(s) *14-24 and 34-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-13,25,27-33 and 37-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/16/04 and 3/4/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments filed on 3/4/04 and 4/8/04 have been entered.

Amended claims 1, 3-13, 25, 27-32 and 37-42 are examined on the merits herein. Additionally, Applicant elected the following species: (a) "targeting molecules" as an additional complexing agent; and (b) "penton protein" as a species of a viral protein.

Response to Amendment

The art rejections of record are withdrawn in light of Applicants' amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 1, 3-13 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of transfecting a eukaryotic cell, said method comprising the method steps recited in claims 1, 12, 13 or 37, does not reasonably provide enablement for a method of transfecting any cell, including a prokaryotic cell as encompassed by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. **This is a new ground of rejection.**

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The instant specification is not enabled for the present broadly claimed invention for the following reasons.

(1) The breadth of the claims.

The claims are drawn to a method of transfecting any cells, including both eukaryotic and prokaryotic cells, by contacting the cells with a nucleic acid in a transfection complex immobilized on a surface.

(2) The state and the unpredictability of the prior art.

At about the effective filing date of the present application, the art on introducing DNA of interest that is immobilized on a multi-well surface into any cells (or reverse transfection method), let alone prokaryotic cells, was relatively nascent (Sabatini, U.S. Patent No. 6,544,790 IDS; Ziauddin et al., Nature 411:107-110, 2001). Additionally, it is uncommon in the prior art that prokaryotic or bacterial cells are transformed or transfected by simply being in contact with any nucleic acid molecule in a transfection complex, particularly since it is well known that prokaryotic cells possess a tough protective cell coat or cell wall, let alone the nucleic acid complex is immobilized on a

surface. Furthermore, it should be noted that the physiological art is recognized as unpredictable (MPEP 2164.03).

(3) The amount of direction or guidance provided.

Apart from the exemplification showing that eukaryotic cells are capable of being transfected by the methods of the presently claimed invention, the instant specification fails to provide sufficient guidance for a skilled artisan on how to transfect any prokaryotic cells in the same manner. It is not clear whether prokaryotic cells behave in the same manner as eukaryotic cells, so that they can also be transfected upon simply contacting the prokaryotic cells with a nucleic acid in a transfection complex immobilized on a surface. Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the present application to do so. Given the lack of sufficient guidance provided by the present disclosure and in light of the state of the prior art discussed above, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

(4) Working examples.

There is no example in the present disclosure showing that bacterial cells or prokaryotic cells are also capable of being transfected under any culture conditions by an immobilized nucleic acid molecule in the form of any transfection complex.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issue set forth above, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-4, 9-11, 25, 27-28 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by Sabatini (U.S. 6,544,790; Cited previously). **This is a new ground of rejection.**

Sabatini teaches a method to create transfected eukaryotic cell microarrays that are suitable for rapidly screening large sets of cDNAs or DNA constructs for those encoding desired products or for causing cellular phenotypes of interest (See Summary of the Invention, cols. 1-6). In one embodiment, the method comprises a mixture comprising a DNA of interest and a carrier protein (e.g., gelatin or fibronectin in water), being deposited onto a surface (e.g., a slide, bottoms of wells in a multi-welled plate including a 96-well plate, see Fig. 5C) in defined, discrete locations or spots and the resulting product is allowed to dry. **Please note that eukaryotic cells express receptors that bind to gelatin and/or fibronectin, and therefore gelatin or fibronectin is a ligand for a receptor** (first complexing agent). After drying, the surface bearing the spots is covered with an appropriate amount of a lipid-based

transfection reagent (e.g., Lipofectamine, col. 10, line 1; third complexing agent), and the resulting product is incubated under conditions appropriate for complex formation between the DNA in the spots and the lipid-based transfection reagent. Subsequent to a washing step, eukaryotic cells in an appropriate medium are plated onto the surface, and the resulting product is maintained under conditions that result in entry of the DNA into plated cells (col. 2 line 1 continues to line 30 of col. 3). Sabatini also teaches that the surface (e.g., a slide) can also be coated for example with poly-L-lysine, a cationic molecule (col. 2, lines 49-52; col. 10 lines 42-46, second complexing agent). In a second embodiment, the method comprises a mixture comprising a DNA of interest, a carrier protein (gelatin or fibronectin), a sugar (can also be considered as a complexing agent), a buffer that facilitates DNA condensation and an appropriate lipid-based transfection reagent (e.g., Lipofectamine, col. 10, line 1) being spotted onto a surface in defined locations, and the resulting product is allowed to dry prior to the plating of eukaryotic cells on top of the drying surface (col. 3, line 32 continues to line 21 of col. 4).

Sabatini teaches specifically that the transfection mixture can be one made from available components or can be a commercially available mixture, such as Effectene, Fugene or Lipofectamine, and that it is added in an appropriate quantity which can be determined empirically, taking into consideration the amount of DNA in each defined location (col. 9, line 64 continues to line 4 of col. 10).

Sabatini discloses that aforementioned reverse transfection and expression of the encoded product or effect of the introduced DNA can be assessed by known

methods such as immunofluorescent detection, enzyme immunocytochemistry, autoradiography, *in situ* hybridization and others (col. 4, lines 22-46).

Accordingly, the teachings of Sabatini meet every limitation of the instant claims. Therefore, the reference anticipates the presently claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5-6, 8, 12, 25, 27, 29, 31-32, 38-40 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabatini (U.S. 6,544,790; IDS) in view of Hawley-Nelson et al. (US 5,736,392). **This is a new ground of rejection.**

Sabatini teaches a method to create transfected eukaryotic cell microarrays that are suitable for rapidly screening large sets of cDNAs or DNA constructs for those encoding desired products or for causing cellular phenotypes of interest (See Summary of the Invention, cols. 1-6). In one embodiment, the method comprises a mixture comprising a DNA of interest and a carrier protein (e.g., gelatin or fibronectin), being deposited onto a surface (e.g., a slide, bottoms of wells in a multi-welled plate including a 96-well plate, see Fig. 5C) in defined, discrete locations or spots and the resulting product is allowed to dry. **Please note that eukaryotic cells express receptors that bind to gelatin and/or fibronectin, and therefore gelatin or fibronectin is a ligand for a receptor**. After drying, the surface bearing the spots is covered with an appropriate amount of a lipid-based transfection reagent (e.g., Lipofectamine, col. 10, line 1), and the resulting product is incubated under conditions appropriate for complex formation between the DNA in the spots and the lipid-based transfection reagent. Subsequent to a washing step, eukaryotic cells in an appropriate medium are plated onto the surface, and the resulting product is maintained under conditions that result in entry of the DNA into plated cells (col. 2 line 1 continues to line 30 of col. 3). Sabatini also teaches that the surface (e.g., a slide) can also be coated for example with poly-L-lysine, a cationic molecule (col. 2, lines 49-52; col. 10 lines 42-46). In a second embodiment, the method comprises a mixture comprising a DNA of interest, a carrier protein (gelatin or fibronectin), a sugar (can also be considered as a complexing agent), a buffer that facilitates DNA condensation and an appropriate lipid-based transfection reagent (e.g., Lipofectamine, col. 10, line 1) being spotted onto a surface in defined

locations, and the resulting product is allowed to dry prior to the plating of eukaryotic cells on top of the drying surface (col. 3, line 32 continues to line 21 of col. 4).

Sabatini teaches specifically that the transfection mixture can be one made from available components or can be a commercially available mixture, such as Effectene, Fugene or Lipofectamine, and that it is added in an appropriate quantity which can be determined empirically, taking into consideration the amount of DNA in each defined location (col. 9, line 64 continues to line 4 of col. 10).

Sabatini discloses that aforementioned reverse transfection and expression of the encoded product or effect of the introduced DNA can be assessed by known methods such as immunofluorescent detection, enzyme immunocytochemistry, autoradiography, *in situ* hybridization and others (col. 4, lines 22-46).

Sabatini et al. do not specifically teach that the transfection complex comprising penton protein as a ligand for a receptor (the elected species) or the ligand is covalently linked to a cationic protein or that the transfection complex further comprising targeting molecules or one or more cationic lipids as additional complexing agents.

However, at the effective filing date of the present application Hawley-Nelson et al. already teach a cationic lipid composition comprising a receptor-ligand peptide (e.g., a penton base coat protein of an adenovirus, RGD peptides, peptides that bind to receptor molecules that are specifically expressed in limited cell types and others including nuclear localization peptides) conjugated to a DNA-binding group (e.g, polyamine, spermine), wherein the peptide is non-covalently associated with a nucleic acid to form a complex which is further combined with a cationic lipid (e.g.,

Lipofectamine), wherein the cationic lipid composition shows an enhanced transfection efficiency in eukarytic cells over the cationic lipid alone (col.5 -col. 9, particularly line 7 of col. 7 continues to line 34 of col. 8, and Figures 8-9). Hawley-Nelson et al. further teach that the cationic lipid composition can also comprise a mixture of cationic lipids (col. 9, lines 1-4).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the method taught by Sabatini by utilizing the transfection mixture of Hawley-Nelson et al instead of Lipofectamine per se to enhance the transfection efficiency in eukaryotic cells in light of the teachings of Hawley-Nelson et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Hawley-Nelson et al. teach specifically that that the cationic composition comprising a penton base coat protein of an adenovirus as a receptor ligand and/or a nuclear localization peptide has an enhanced transfection efficiency in eukaryotic cells over the cationic lipid such as Lipofectamine alone. Moreover, Sabitini teaches that the transfection mixture can be one made from available components or can be a commercially available mixture, indicating that the method of Sabitini is not limited to any particular transfection mixture. Furthermore, Applicants also teach that the term "ligand for receptors" refers to a first molecule, the ligand, which is able to bind to a second molecule, such as a protein, sugar or lipid, which is associated with a cell membrane, and examples of such ligands include but are not limited to transferrin and low density lipoprotein particles, which bind to LDL receptors, and viral proteins that are known to bind to integrins (see specification, page 32, lines 6-13), and that "cationic

proteins include but are not limited to polylysines, histones, transcripition factors, polyhistidines, polyarginines, spermines, and spermidines (page 55, lines 4-6).

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Sabatini et al., Hawley-Nelson et al., and a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Claims 6, 13, 30 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabatini (U.S. 6,544,790; IDS) in view of Hawley-Nelson et al. (US 5,736,392) as applied to claims 1, 3, 5-6, 8, 12, 25, 27, 29, 31-32, 38-40 and 42 above, and further in view of Wagner et al. (Proc. Natl. Acad Sci USA 89:7934-7938, 1992, IDS). **This is a new ground of rejection.**

The teachings of Sabatini and Hawley-Nelson et al. have been discussed above. However, none of the reference teaches specifically that the transfection complex comprising transferrin as a ligand and polylysine as a cationic protein.

However, at the effective filing date of the present application Wagner et al. already teach transferrin-polylysine-DNA complexes have been successfully used to deliver exogenous genes to eukaryotic cells expressing transferrin receptors via receptor-mediated endocytosis mechanism (see abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to further modify the method taught by Sabatini and Hawley-Nelson et al. by utilizing the

transfection mixture containing transferrin as a ligand and polylysine as a cationic protein for transforming eukaryotic cells expressing transferrin receptors in light of the teachings of Wagner et al.

An ordinary skilled artisan would have been motivated to carry out the above modification to transform eukaryotic cells expressing transferrin receptors, and that the transferrin-polylysine-DNA complexes have been successfully used to deliver exogenous genes to those cells. Additionally, Sabitini teaches that the transfection mixture can be one made from available components or can be a commercially available mixture, indicating that the method of Sabitini is not limited to any particular transfection mixture. Furthermore, Hawley-Nelson et al. teach that a receptor ligand peptide in the transfection complex can include any peptide that has an affinity for or binding to receptor molecules that are broadly expressed in a variety of cell types or one that bind to receptor molecules that are specifically expressed in a limited number of cell types (col. 8, lines 24-34), and that the "DNA-binding group" includes any protein, any peptide, polypeptide or polyamine which is capable of binding nucleic acid (col. 6, lines 62-65).

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Sabatini et al., Hawley-Nelson et al., and Wagner et al. and a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-4, 8-12, 25, 27-28 and 37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-15 of copending Application No. 10/123,435. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of transfecting eukaryotic cells of the copending Application has the same method steps and similar starting materials (cationic lipid, a ligand for a receptor and a cationic protein as complexing agents in an immobilized nucleic acid complex) as the methods of the present application. Additionally, the method in the co-pending applciation anticipates the claimed genus in the application being examined (with respect to cell types and membrane permeable molecule) and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub- should the genus issue as a patent after the species of sub-genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER